6. **The information pertaining to a new diagnosis of rheumatic disease by a rheumatologist is either incomplete or requires clarification. Please provide the following information:**

   a. **The information in Section 5.4.11 of the Core Study Clinical Data Report conflicts with the values provided in Table 8.7.1 regarding new diagnoses of rheumatic disease. Please rectify this discrepancy.**

      6a Response:

      We acknowledge that there is a discrepancy between Section 5.4.11 and Table 8.7.1. This has been corrected in the attached 3-Year Core Gel Clinical Study Update. Please note that there was a total of six patients who reported a new diagnosis of rheumatic disease as determined by a rheumatologist.

   b. **For each of the patients reporting a new diagnosis of rheumatic disease, please provide the following information:**

      (1) type of implant and type of placement;

      (2) duration following breast implantation for diagnosis;

      (3) a summary of the results of signs, symptoms, and laboratory tests pertinent to the diagnosis;

      (4) copies of all physician notes and laboratory tests pertinent to the diagnosis;

      (5) nature and timing of reported local complications, if any, in these patients;

(6) rupture status of the implants, including results of MRI screening for rupture; and

(7) the specific type of "other" inflammatory arthritis in the augmentation patient reported in Table 11.1.

6b Response:

There were six patients, none of whom had ruptures, who were diagnosed with a new rheumatic disease after enrollment in the Core Gel Study. The observed incidence rate of these diseases in the Core Study was below that of the general US population (the estimated incidence of thyroiditis (including Hashimoto and other) and rheumatoid arthritis is reported to be 0.8% and 0.9%, respectively,[52/] the incidence of fibromyalgia is reported to be 3.4%,[53/] and the incidence of pyoderma gangrenosum is reported to be 0.6% (in patients with ileostomy and inflammatory bowel disease[54/]). The findings in the present study are consistent with the lack of association between silicone breast implants and connective tissue and rheumatic diseases demonstrated in numerous epidemiological studies.

The table below summarizes their diagnoses and rupture status. Copies of the rheumatology consults on these patients can be found in Attachment 20. The consults summarize the signs, symptoms and laboratory tests pertinent to the diagnosis. None of the patients were part of the MRI substudy, and only one patient, 405-038 had a MRI "for cause," which revealed no rupture.

The diagnosis of Augmentation patient [redacted] ied to be hypothyroidism and is reflected in the table below.

52/ Jacobson, D.L., et al. 1997. Epidemiology and estimate population burden of selected autoimmune diseases in the United States. *Clin Immunol. Immunopathol.* 84(3):223-43.

49/ Wolfe, F., K. Ross, J. Anderson, I.J. Russell and L. Hebert. 1995. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 38(1):19-28.

54/ Mancini, G.J., et al. 2002. Parastomal pyoderma gangrenosum: a case report and literature review. *Am Surg.* 68(9):824-6.

New Diagnoses of Connective Tissue, Rheumatoid, and Autoimmune Disease

Pt. ID	Patient Information	Diagnosis	Time to Onset of Diagnosis	Rupture status	Summary	Adverse Events
	Cohort: Augmentation **DOS** **Implant Type:** textured round gel **Placement:** subglandular **MRI Substudy:** YES **MRI Scan Dates:** **Investigator**	Hashimoto's Thyroiditis	17 months (date reported . April 2002)	No rupture	Hashimoto's thyroiditis diagnosed at 2 year visit. Documented with rheumatology consult	new diagnosis of rheumatic disease R- unac low nipple sensit
	Cohort: Augmentation **DOS:** **Implant Type:** smooth round gel **Placement:** subglandular **MRI Substudy:** NO **MRI Scan Dates** **Investigator:**	Rheumatoid arthritis	19 months (date reported May 2003)	No rupture	At her two year visit, this patient reported multiple symptoms and she was referred to a rheumatologist Doctor's notes state the patient says she probably had symptoms prior to surgery, although she did not report any at her baseline visit. Reported seronegative rheumatoid arthritis at 2 year visit.	New diagnosis of rheumatic disease 5/2003 Bilateral Baker III capsular contr
	Cohort: Augmentation **Implant Type:** smooth round gel **Placement:** subpectoral **MRI Substudy:** NO **MRI Scan Dates:** n/a **Investigator:**	Hypothyroidism	32 months (date reported: June 2002)	Not scanned	At the two year visit, this patient reported multiple symptoms and she was referred to a rheumatologist Rheumatoid arthritis reported at 2 year visit. Arthritis not mentioned in 2-year rheumatology consult. Consult was reviewed by a rheumatology expert who indicated patient had hypothyroidism and as a result has thyroiditis, which is autoimmune in origin	New diagnosis of rheumatic disea
	Cohort: Revision **DOS** **Implant Type:** textured round gel **Placement:** submuscular **MRI Substudy:** YES **MRI Scan Dates:** **Investigator.**	Fibromyalgia	12 months (date reported: 2002)	No rupture	At her two year visit, this patient reported multiple symptoms and she was referred to a rheumatologist who confirmed diagnosis of fibromyalgia	New diagnosis of rheumatic

Pt. ID	Patient Information	Diagnosis	Time to Onset of Diagnosis	Rupture status	Summary	Adverse Events
[illegible]	**Cohort:** Revision**DOS:** **Implant Type:** smooth round gel **Placement:** submuscular **MRI Substudy:** NO **MRI Scan Dates:** n/a **Investigator:** C[illegible]	Pyoderma gangrenosum	12 months(date reported June 2002)	No scan	Pyoderma gangrenosum diagnosed at 1 year Dermatologist treating her with steroids for pyoderma gangrenosum A rheumatology expert reviewed the documents and said this patient could have an autoimmune disease, and it is usually associated with IBS or Crohn's disease To be conservative, it is being reported as a new diagnosis of rheumatic disease	New diagnosis of rheumatic disease 2/2002L Breast pain not associated w other complication 8/9/01Infection 7/30/01
[illegible]	**Cohort:** Reconstruction **DOS:** **Implant Type:** textured round gel **Placement:** submuscular **MRI Substudy:** YES **MRI Scan Dates** **Investigator:** Robert Mirabile	Fibromyalgia	9 months (date reported July 2002)	No rupture	At the 1 year visit, patient reported multiple symptoms and was referred to a rheumatologist who confirmed diagnosis of fibromyalgia	[illegible]

c. **Please indicate the number of patients within each indication which were referred to a rheumatologist and the reason(s) for referral. If there were patients reporting new rheumatologic signs/symptoms or who had new rheumatologic physical examination findings and were <u>not</u> referred to a rheumatologist, please indicate the reason(s) for the lack of referral, as well as what measures will be taken to get a referral in these cases.**

6c Response:

As detailed in the table below, there were eight Augmentation, two Reconstruction, and four Revision patients referred to a rheumatologist. No specific reason for referral was given. As detailed in the protocol and on the Case Report Form, the Investigator is asked, "in his or her medical opinion, do the patient's symptom(s) warrant a rheumatological exam?" If yes, the patient was referred to a rheumatologist

Indication	Number
Augmentation	8
Reconstruction	2
Revision	4
Overall	12

7. The information regarding rheumatologic signs/symptoms is either incomplete or requires clarification. Please provide the information/analyses below.

a. Please list the specific signs/symptoms which correspond to each symptom category.

7a Response:

The specific signs/symptoms that correspond to each symptom category, defined by WHO are delineated in the table below:

Symptom Category	Symptom
Skin and Appendages	Open sores; Severe rashes; Severe dryness of skin; Frequent hives; Tightness of skin; Unusual hair loss
Muscle	Heel pain; Frequent muscle cramps; Neck pain/stiffness; Frequent muscle pain; Jaw pain; Back pain/stiffness,
Joint	Joint swelling; Joint pain
CNS	Insomnia; Numbness of feet; Numbness of hands
Gastrointestinal	Pain on swallowing or chewing; Loss of appetite; Difficulty swallowing; Frequent, severe or persistent diarrhea or constipation
Body as a Whole	Fatigue; Weakness; Exhaustion; Dryness of eyes, nose; Persistent fever; Night sweats; Generalized aching; Loss of height; Dryness of mouth; Severe chest pains; Tender lumps/bumps; Excessive sensitivity to sun; Color changes on hands or feet with cold exposure; Tenderness of scalp
Metabolic and Nutritional	Loss of weight without dieting
Hearing and Vestibular	Ringing in ears
Respiratory	Pain on breathing; Chronic cough
Platelet, Bleeding, Clotting Disorder	Severe bruising with little or no injury
Cardiovascular	Heart murmurs
Vision	Pain/grittiness in eyes; Redness of eyes

b. In an attempt to interpret these data, the statistical analyses described below are necessary for specific data sets. The six data sets include:

- **each individual symptom category;**
- **each individual sign/symptom;**
- **each individual physical examination finding;**
- **"combined fatigue" sign/symptoms (for example, a patient reporting either fatigue, exhaustion, or weakness);**

- **"combined pain" signs/symptoms (for example, a patient reporting either frequent muscle cramps, neck pain/stiffness, generalized aching, joint pain, frequent muscle pain, back pain/stiffness, or frequent muscle cramps); and**

- **"combined fibromyalgia" signs/symptoms (a patient having at least one of the "combined fatigue" signs/symptoms and at least one of the "combined pain" signs/symptoms).**

Please provide the statistical analyses below on each of the six data sets above.

(1) Please provide a comparison to the data from your saline-filled breast implant.

7b (1) Response:

A comparison table between Mentor's Core gel and Saline-filled breast implant (SPS) rheumatologic symptoms data are presented in Table 11.10 in Attachment 21. The comparison for rheumatologic symptoms by system category is presented in Table 11.11 in Attachment 21. Because of the small number of Core Gel patients who reported rheumatological symptom types, no clinically meaningful comparisons to the saline data can be made. A comparison of physical examination findings is not available as these data were not collected in the Saline (SPS) study.

(2) Please provide an analysis to determine whether these changes are due to increasing covariates such as age, for example. A model that may address this issue is a GEE model that uses the baseline status (presence or absence of the symptom) and the status biennially after implantation as response variables. Age at time of implantation (divided into categories) should be a covariate.

7b (2) Response:

The analysis based on the GEE model, is provided in Table 11.12 in Attachment 22.

(3) Please provide a comparison to published data of similar populations, if any.

7b (3) Response:

The comparison between Mentor's Core gel and the literature is provided in Table 11.14 in Attachment 21. Because of the small number of Core Gel patients who reported rheumatological symptom types, and the differences in study designs, no clinically meaningful comparisons can be made with published literature.

(4) Please provide correlations between new signs/symptoms/physical examination findings and patient dissatisfaction, local complications, and both silent rupture and rupture noted at explantation.

7b (4) Response:

The comparison between new signs/symptoms/physical examination findings and patient dissatisfaction, local complications, and both silent rupture and rupture and the literature is provided in Table 11.13 in Attachment 21. A review of the table reveals there was no correlation between any of these parameters and new rheumatological symptoms.

8. You reported new rheumatological diseases and symptoms in Tables 11.1-11.8. However, you did not provide a summary table which compares the frequency before implantation and 2 years after. Please provide a summary table for the major categories of rheumatological signs and symptoms that reports the frequencies at baseline and 2 years later (or later depending on length of your follow-up submitted in your response).

8 Response:

A comparative frequency of new rheumatological diseases and symptoms through three years is provided in Table 11.9 Attachment 21. The number of reported new symptom types is too low to be able to discern any meaningful trends through three years of implantation.